No CHARTS ATTACHED

TOBACCO INDUSTRY RESEARCH COMMITTEE
150 EAST FORTY SECOND STREET NEW YORK 17, N. Y.

Application For Research Grant #155

Date: March 29, 1957

1. Name of Investigator: Duane G. Venzel

2. Title: Professor of Pharmacology

3. Institution & Address: School of Pharmacy, University of Kansas, Lawrence, Kansas

4. Project or Subject: The determination of the chronic effects of orally administered nicotine on serum cholesterol and phospholipids; the electrocardiographic response to ergonovine; and the vascular pathology of cholesterol-fed rabbits.

5. Detailed Plan of Procedure (Use reverse side if additional space is needed):

Prior Work On This Project The accompanying sheet and graphs summarize the completed pilot study. In brief, the daily administration of 2 mg./Kg. of nicotine in the drinking water of male rabbits fed 0.1% cholesterol in their diets produced a significant increase in the blood cholesterol levels. Work is currently underway using essentially the same experimental procedure with chickens instead of rabbits.

It is proposed that the rabbit study be repeated with certain additions and modifications in order to determine if nicotine increases vascular pathology as well as serum cholesterol levels.

First, female rabbits are to be used instead of male as some male rabbits are refractory to the development of atherosclerosis (1).

Second, the period of study will be extended beyond that of the pilot study as rabbits must be close to one year of age and be kept on a cholesterol diet for at least twenty weeks before vascular pathology appears (2,3).

Third, several levels of nicotine are to be administered in order to obtain evidence either for or against a causal relationship between nicotine and hypercholesterolemia as well as the possible relationship between nicotine and vascular pathology. Doses of 0.125 mg./Kg., 0.5 mg./Kg. and 2.0 mg./Kg. are to be administered to separate groups. The doses were selected on the basis of the report that 4 mg. of nicotine orally in man causes similar psychic effects as smoking one cigarette (4). On a weight basis, a dose of 1.0 mg./Kg. of nicotine represents approximately the equivalent of one package of cigarettes.

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Finally, cardiovascular pathology is to be sought first of all in the living animals throughout the experiment by means of electrocardiographs under ergonovine stress (3). This technique should reveal whether atherosclerosis is demonstrable in the nicotine-cholesterol group prior to the cholesterol group. Vascular pathology will also be studied according to standard histological techniques. This phase of the work will be under the supervision of Dr. Harlan I. Firminger, Professor of Pathology, University of Kansas Medical School, Kansas City, Kansas.

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6. Budget Plan:

Salaries	4,654.00
Expendable Supplies	600.00
Permanent Equipment	785.00
Overhead 15%	905.00
Other	
Total	6,944.00

As expenses will be greatest at the initiation of the work, it is requested that at least 1/2 the amount be made available immediately rather than in quarterly payments.

7. Anticipated Duration of Work:

July 1, 1957 through June 30, 1958.

8. Facilities and Staff Available:

An air-conditioned animal room and completely equipped research laboratories are available for this project. The project director will be available on a full-time basis for two months of the summer and on a part-time basis during the remainder of the year. A one-half time research assistant will work on the project throughout the year. Other personnel whose services will be used include a pathologist, laboratory technician and animal room caretaker. Equipment in the Department of Pharmacology includes a Warburg Manometer, spectrophotometer, oscilloscope and recorder, flame photometer etc.

9. Additional Equipment:

None.

10. Additional Information (Including relation of work to other projects and other sources of supply):

The studies with nicotine and atherosclerosis to date have been paid for primarily by the University of Kansas, however, we are unable to receive further support because of the heavy costs involved.

Keith L. Kitcher
Comptroller
121 Strong Hall
University of Kansas

Signature
/s/ Duane C. Wenzel
Director of Project

/s/ W. J. Argersinger, Jr.
Business Officer of the Institution

Assistant Dean, Graduate School

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PREVIOUS WORK DONE ON THIS PROJECT

Albino, New Zealand, male rabbits were the experimental animals in the study just completed. At six weeks of age four groups of twelve animals per group were arranged as follows:

Group 1. Control----------Fed Purina Rabbit Chow and water ad libitum.
Group 2. Cholesterol----------0.1% cholesterol in above diet.
Group 3. Nicotine----------2 mg./Kg. nicotine daily administered in drinking water.
Group 4. Nicotine-Cholesterol------Combined procedures of groups 2 and 3.

At the onset of the experiment and at monthly intervals thereafter for five months, determinations were made of the total plasma cholesterol and lipid phosphorous. The following values were obtained:

Group — Time in Weeks
Total cholesterol/Lipid phosphorous (mg.%)[1]

	0	4	8	12	16	20
Control	60/6	39/6	35/5	34/3	30/3	43/3
Cholesterol	51/6	120/8	95/7	97/5	99/4	102/5
Nicotine	70/6	57/5	47/6	54/5	58/5	47/4
Cholesterol + nicotine	64/6	107/7	112/7	195/7	195/7	193/8

1 For convenience of comparison values are given in round numbers.

At twenty weeks of age blood levels of vitamin C were determined because of reports that nicotine lowers the blood level of this vitamin. No significant differences were observed between the control and nicotine groups. Studies were also made at this time for the relative serum stability as determined by the turbidity produced upon the addition of a zinc salt. Once again no significant differences were observed. Because of the possible role of the liver in hypercholesterolemia, bromsulfalein was used to evaluate liver function. No conclusive differences were established.

Upon sacrifice a gross examination of the aortas did not indicate any greater incidence of plaques in the experimental animals than in the controls. Microscopic pathology was not determined because of the lack of a qualified pathologist at this time. In the proposed studies to follow, however, the services of Dr. Harlan I. Firminger, Professor of Pathology, are available.

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Duane G. Wenzel

Biography

Born, September 18, 1920.
B.S. Pharmacy, University of Wisconsin 1942.
Ph.D. Pharmacology and Pharmaceutical Chemistry 1948, University of Wisconsin.
Assistant Professor of Pharmacology, School of Pharmacy, U. of Kansas 1948.
Associate Professor of Pharmacology, School of Pharmacy, U. of Kansas 1952.
Professor of Pharmacology, School of Pharmacy, U. of Kansas 1956.
Associate editor, Midwestern Druggist, 1948 -----.
Committee on Physiological Testing, American Pharmaceutical Association, 1956-59.

Scientific Bibliography

Actions of Podophyllin Derivatives, Fed. Proc., 7, 1 (1948).

A Study of the Toxicity and Anthelmintic Activity of n-Butylidene Chloride, J. Pharm. Pharmacol., 3, 169 (1951).

Osageorange Oil, Trans. Kans. Acad. Sci., 54, 94 (1951).

Pharmacological Actions of Paeonia officinalis, J. Am. Pharm. Assoc., 41, 162 (1952).

The Effect of Antipyretics on the Erythrocytic Sedimentation Rate of Rats, J. Am. Pharm. Assoc., 42, 600 (1953).

Cardiac Activity of Unsaturated Lactones as Related to Their Theoretical Peroxide Formation, J. Am. Pharm. Assoc., 42, 653 (1953).

Central Depressant Properties of Uracil and Related Oxypyrimidines, J. Am. Pharm. Assoc., 44, 56 (1955).

Anticonvulsant Activity of Some Uracils and Related Compounds, 44, 550 (1955).

The Evaluation of Arsenic as an Antiasthmatic I. Effect on Experimental Asthma of Guinea Pigs, J. Am. Pharm. Assoc., 45, 1 (1956).

The Evaluation of Arsenic as an Antiasthmatic II. A study of Possible Mechanisms, J. Am. Pharm. Assoc., 45, 6 (1956).

An Investigation of Triterpenes as Steroid Hormones, J. Am. Pharm. Assoc., 45, 284 (1956).

Estrogenic Activity of Some Flavonoids, J. Am. Pharm. Assoc., 45, 367 (1956).

The Effect of Triterpenes on the Excretion of Sodium and Potassium by Rats, J. Am. Pharm. Assoc., 45, 372 (1956).

Antispasmodic and Related Pharmacological Actions of Some γ-Arylpropylamines, J. Am. Pharm. Assoc., 45, 414, (1956).

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Scientific Bibliography (Cont.)

Anticonvulsant Properties of Some Alkyldiols, Alkyldiones and Related Compounds, J. Am. Pharm. Assoc,, 45, 669 (1956).

Central Stimulating Properties of Some Terpenones, J. Am. Pharm. Assoc., 46, 77 (1957).

Studies Completed or in Press

The Effect of Nicotine on Experimental Hypercholesterolemia in the Rabbit

The Antiveratrinic Action of Some Simple Lactones and Peroxides

The Effect of BAL on the Amine Oxidase/Decarboxylase Ratio of the Kidneys of Normal and Renal Hypertensive Rats

The Relationship of Electroshock and Anticonvulsants to Brain Succinic Dehydrogenase

Anthelmintic Activity of Peroxide-Forming Compounds

Pharmacological Actions of Optical Isomers of Some Phosphonamidates

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